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CLAIMS

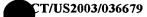
What is claimed:

- 1. A method of preventing bone metastases comprising administering to a subject afflicted with metastatic cancer a therapeutically effective amount of M-CSF antagonist thereby preventing bone loss associated with the metastatic cancer.
- 2. A method of treating a subject afflicted with a metastatic cancer to bone comprising administering to said subject a therapeutically effective amount of M-CSF antagonist thereby reducing the severity of bone loss associated with the metastatic cancer.
- The method according to claims 1 or 2 wherein said subject is a mammal.
 - 4. The method according to claim 3 wherein said mammal is human.
 - 5. The method according to claim 4 wherein said antagonist inhibits the interaction between M-CSF and its receptor (M-CSFR).
- 6. The method according to claim 5 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.
 - 7. The method according to claim 5 wherein said M-CSF antagonist is selected from the group consisting of:
 - a) a polypeptide comprising an anti-M-CSF antibody;
 - b) a polypeptide comprising an anti-M-CSFR antibody thereof;
 - c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; or
 - d) a soluble polypeptide comprising an M-CSFR mutein or derivative thereof.
- 8. The method according to claim 7 wherein said M-CSF antagonist is an anti-M-CSF antibody.
 - 9. The method according to claim 7 wherein said M-CSF antagonist is a polypeptide comprising an anti-M-CSFR antibody.
 - 10. The method according to claim 7 wherein said M-CSF antagonist is a soluble polypeptide comprising an M-CSF mutein or derivative thereof.
- The method according to claim 7 wherein said M-CSF antagonist is a soluble polypeptide comprising an M-CSFR mutein or derivative thereof.
 - 12. The method according to claim 8 or 9 wherein said antibody is selected

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from the group consisting of:

- a) a polyclonal antibody;
- b) a monoclonal antibody;
- c) a humanized antibody;
- d) a human antibody;
- e) a chimeric antibody;
- f) Fab, F(ab')₂ or F_v antibody fragment; and
- g) a mutein of any one of a) to f).
- 13. The method according to claim 8 wherein the antibody binds to the same epitope as monoclonal antibody 5H4 (ATCC Accession No. HB10027).
 - breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer.
 - 15. The method according to claim 8 wherein the M-CSF antagonist is an antibody administered at a dose between about 0.01 mg/kg and about 100 mg/kg.
 - 16. A non-murine antibody that binds to M-CSF for treating a subject afflicted with a metastatic cancer, wherein said antibody effectively reduces the severity of bone loss associated with the metastatic cancer.
- 17. A non-murine monoclonal antibody that specifically binds to the same epitope of M-CSF as monoclonal antibody 5H4.
 - 18. A non-murine monoclonal antibody that competes with monoclonal antibody 5H4 for binding to M-CSF more than 75%.
 - 19. A non-murine antibody that binds to M-CSFR for treating a subject afflicted with a metastatic cancer, wherein said antibody effectively reduces the severity of bone loss associated with the metastatic cancer.

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- 20. The antibody according to claim 16 wherein said antibody is selected from the group consisting of:
 - a) a polyclonal antibody;
 - b) a monoclonal antibody;
 - c) a humanized antibody;
 - d) a human antibody;
 - e) a chimeric antibody;
 - f) Fab, F(ab')₂ or F_v antibody fragment; and
 - g) a mutein of any one of a) to f).
- 10 The antibody according to claim 20 wherein the antibody is specific to 21. M-CSF.
 - 22. The antibody according to claim 20 wherein the antibody is specific to M-CSFR.
- The antibody according to claim 20 wherein said antibody is a fully 23. 15 human antibody.
 - 24. The antibody according to claim 20 wherein said antibody is a humanized antibody.
 - 25. A hybridoma that secretes an antibody according to claim 23.
- The antibody according to claim 20 wherein the cancer is breast, lung, 26. renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, 20 including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer. 25
 - 27. A pharmaceutical composition comprising any one of the antibodies of claims 17 to 26, and a pharmaceutically suitable carrier, excipient or diluent.
 - 28. A method of screening for an M-CSF antagonist comprising the steps of:
 - a) contacting metastatic tumor cell medium, osteoclasts and a

candidate antagonist;

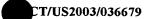
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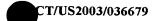
- b) detecting osteoclast formation, proliferation and/or differentiation; and
- c) identifying said candidate antagonist as an M-CSF antagonist if a
 decrease in osteoclast formation, proliferation and/or differentiation is detected.
 - 29. The method of claim 28 wherein said metastatic tumor cell medium includes tumor cells.
 - 30. The method of claim 28 wherein said contacting step (a) occurs in vivo, said detecting step (b) comprises detecting size and/or number of bone metastases, and said candidate antagonist is identified as an M-CSF antagonist if a decrease in size and/or number of bone metastases is detected.
 - 31. The method of claim 28 further comprising the step of determining if said candidate antagonist binds to M-CSF.
 - 32. The method of claim 28 further comprising the step of determining if said candidate antagonist inhibits interaction between M-CSF and its receptor M-CSFR.
 - 33. The method according to claim 28 wherein said candidate antagonist is selected from the group consisting of:
 - a) a polypeptide comprising an anti-M-CSF antibody;
 - b) a polypeptide comprising an anti-M-CSFR antibody thereof;
 - c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof:
 - d) a soluble polypeptide comprising an M-CSFR mutein or derivative thereof;
 - e) a peptide; or
 - f) a small molecule.
 - 34. The method according to claim 33 wherein said candidate antagonist is an M-CSF mutein.
 - 35. The method according to claim 33 wherein said candidate antagonist is an M-CSFR mutein.
- 36. The method according to claim 33 wherein said candidate antagonist is

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an anti-M-CSF antibody.

- 37. The method according to claim 33 wherein said candidate antagonist is an anti-M-CSFR antibody.
- 38. A method of identifying an M-CSF antagonist that can prevent or treat metastatic cancer to bone, comprising the steps of:
 - (a) detecting binding of a candidate antagonist to M-CSF; and
 - (b) assaying the ability of said candidate antagonist to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.
- 39. A method of identifying an M-CSF antagonist that can prevent or treat metastatic cancer to bone, comprising the steps of:
 - (a) detecting binding of a candidate antagonist to M-CSFR; and
 - (b) assaying the ability of said candidate antagonist to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.
 - 40. A method of identifying an M-CSF antagonist that can prevent or treat metastatic cancer to bone, comprising the steps of:
 - (a) identifying a candidate antagonist that inhibits the interaction between M-CSF and M-CSFR; and
 - (b) assaying the ability of said candidate antagonist to prevent or treat metastatic cancer to bone *in vitro* or *in vivo*.
- 41. A method of preventing bone metastases and tumor growth comprising administering to a subject afflicted with metastatic cancer therapeutically effective amounts of M-CSF antagonist and a therapeutic agent, thereby preventing bone loss associated with the metastatic cancer and preventing tumor growth.
- 42. A method of treating a subject afflicted with a metastatic cancer
 comprising administering to said subject therapeutically effective amounts of M-CSF
 antagonist and a therapeutic agent, thereby reducing the severity of bone loss associated with
 the metastatic cancer and inhibiting tumor growth.
 - 43. The method according to claims 41 or 42 wherein said subject is a mammal.
 - 44. The method according to claim 43 wherein said mammal is human.





- 45. The method according to claim 44 wherein said antagonist inhibits the interaction between M-CSF and its receptor M-CSFR.
- 46. The method according to claim 41 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.
- 47. The method according to claim 45 wherein said M-CSF antagonist is selected from the group consisting of:
 - a) a polypeptide comprising an anti-M-CSF antibody;
 - b) a polypeptide comprising an anti-M-CSFR antibody thereof;
 - c) a soluble polypeptide comprising an M-CSF mutein or derivative

10 thereof; and

thereof.

d) a soluble polypeptide comprising an M-CSFR mutein or derivative

48. The method according to claim 47 wherein said antibody is selected from the group consisting of:

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- a) a polyclonal antibody;
- b) a monoclonal antibody;
- c) a humanized antibody;
- d) a human antibody;
- e) a chimeric antibody;

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- f) Fab, F(ab')2 or F_v antibody fragment; and
- g) a mutein of any one of a) to f).
- 49. The methods according to claims 41 or 42 wherein the therapeutic agent is a bisphosphonates.
- 50. The method according to claim 49 wherein the bisphonate is zeledronate, pamidronate, clodronate, etidronate, tilundronate, alendronate, or ibandronate.
 - 51. The methods according to claims 41 or 42 wherin the therapeutic agent is a chemotherapeutic agent.
 - 52. The method according to claim 51 wherein the subject is precluded from receiving bisphophonate treatment.
 - 53. The methods according to claims 41 or 42 wherein the M-CSF



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antagonist is effective to reduce the dosage of therapeutic agent required to achieve a therapeutic effect.

- 54. The methods according to claims 41 or 42 further comprising the step of administering a non-M-CSF colony stimulating factor, for example G-CSF.
- 55. A pharmaceutical composition comprising a M-CSF antagonist and a cancer therapeutic agent.
- 56. A package, vial or container comprising a medicament comprising an M-CSF antagonist and instructions that the medicament should be used in combination with surgery or radiation therapy.
- 57. A method of preventing or treating metastatic cancer to bone comprising the steps of administering an M-CSF antagonist to a subject and treating said subject with surgery or radiation therapy.
 - 58. A method of targeting a tumor cell expressing membrane-bound M-CSF on its surface comprising the step of administering an antibody that specifically binds to the extracellular portion of membrane-bound M-CSF.
 - 59. The method of claim 58 wherein said antibody is conjugated to a radionuclide or other toxin.
 - 60. The method of claim 59 wherein said antibody is selected from the group consisting of:

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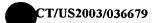
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- a) a polyclonal antibody;
- b) a monoclonal antibody;
- c) a humanized antibody;
- d) a human antibody;
- e) a chimeric antibody;

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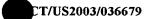
- f) Fab, F(ab')₂ or F_v antibody fragment; and
- g) a mutein of any one of a) to f).
- 61. A method of treating a subject suffering from a cancer, wherein the cells comprising said cancer do not secrete M-CSF, comprising the step of administering an M-CSF antagonist.
 - 62. A method of preventing bone metastases comprising administering to a



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subject afflicted with metastatic cancer an amount of M-CSF antagonist effective to neutralize M-CSF produced by the subject's cells, said amount being larger than the amount effective to neutralize M-CSF produced by the cancer cells.

- 63. A method of treating a subject afflicted with a metastatic cancer to bone comprising administering to said subject an amount of M-CSF antagonist effective to neutralize M-CSF produced by the subject's cells, said amount being larger than the amount effective to neutralize M-CSF produced by the cancer cells.
 - 64. The antibody of any one of claims 16-25, for use in medicine.
- 65. Use of a M-CSF antagonist in the manufacture of a medicament for preventing bone metastases in a subject afflicted with metastatic cancer.
 - 66. Use of a M-CSF antagonist in the manufacture of a medicament for preventing, in a subject afflicted with metastatic cancer, bone loss associated with the cancer.
 - 67. Use of a M-CSF antagonist in the manufacture of a medicament for treating a subject afflicted with a metastatic cancer to bone.
- 15 68. Use of a M-CSF antagonist in the manufacture of a medicament for reducing, in a subject afflicted with a metastatic cancer to bone, the severity of bone loss associated with the cancer.
 - 69. The use according to claims 65-68 wherein said subject is a mammal.
 - 70. The use according to claim 69 wherein said mammal is human.
 - 71. The use according to claim 70 wherein said antagonist inhibits the interaction between M-CSF and its receptor (M-CSFR).
 - 72. The use according to claim 71 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.
- 73. The use according to claim 71 wherein said M-CSF antagonist is selected from the group consisting of:
 - a) a polypeptide comprising an anti-M-CSF antibody;
 - b) a polypeptide comprising an anti-M-CSFR antibody thereof;
 - c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; or
 - d) a soluble polypeptide comprising an M-CSFR mutein or derivative



thereof.

- 74. The use according to claim 73 wherein said antibody is selected from the group consisting of:
 - a) a polyclonal antibody;

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- b) a monoclonal antibody;
- c) a humanized antibody;
- d) a human antibody;
- e) a chimeric antibody;
- f) Fab, F(ab')2 or F_v antibody fragment; and
- g) a mutein of any one of a) to f).

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- 75. The use according to claim 74 wherein the antibody is specific to M-
- 76. The use according to claim 75 wherein the antibody is antibody 5H4.
- 77. The use according to claim 74 wherein the antibody is specific to M-

CSFR.

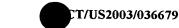
CSF.

- 78. The use according to claim 73 wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia and lymphoma; head and neck cancers; gastrointestinal cancers, including stomach cancer, colon cancer, colorectal cancer, pancreatic cancer, liver cancer; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers and cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; and skin cancer, including malignant melanoma or squamous cell cancer.
- 79. The use according to claims 65-68 wherein the M-CSF antagonist is an antibody administered at a dose between about 0.01 mg/kg and about 100 mg/kg.
- 25 80. Use of the antibody of any one of claims 16-25 in the manufacture of a medicament for treating a subject afflicted with metastatic cancer.
 - 81. Use of the antibody of any one of claims 16-25 in the manufacture of a medicament for reducing, in a subject afflicted with a metastatic cancer, the severity of bone loss associated with the cancer.
- 30 82. Use of a M-CSF antagonist and a therapeutic agent in the manufacture

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of a medicament for preventing, ina subject afflicted with metastatic cancer, bone metastases and tumor growth.

- 83. Use of a M-CSF antagonist and a therapeutic agent in the manufacture of a medicament for preventing, in a subject afflicted with metastatic cancer, bone loss associated with the cancer.
- 84. Use of a M-CSF anagonist and a therapeutic agent in the manufacture of a medicament for treating a metastatic cancer.
- 85. Use of a M-CSF antagonist and a therapeutic agent in the manufacture of a medicament for reducing the severity of bone loss associated with the cancer and inhibiting tumor growth in a subject afflicted with metstatic cancer.
- 86. Product comprising an M-CSF antagonist and a therapeutic agent as a combined preparation for simultaneous, separate or sequential use in treating cancer.
- 87. Use of an M-CSF antagonist in preparation of a medicament for preventing or treating metastatic cancer to bone, wherein the medicament is simultaneously separately or sequentially administered with a cancer therapeutic agent.
- 88. Use of a cancer therapeutic agent in preparation of a medicament for preventing or treating metastatic cancer to bone, wherein the medicament is simultaneously separately or sequentially administered with an M-CSF antagonist.
- A package, vial or container comprising a medicament comprising an
 M-CSF antagonist and instructions that the medicament should be used in combination with surgery or radiation therapy.
 - 90. The use according to claims 82-85 wherein said subject is a mammal.
 - 91. The use according to claim 86 wherein said mammal is human.
- 92. The use according to claim 90 wherein said antagonist inhibits the interaction between M-CSF and its receptor M-CSFR.
 - 93. The use according to claims 82-85 wherein said antagonist inhibits osteoclast proliferation and/or differentiation induced by tumor cells.
 - 94. The use according to claim 92 wherein said M-CSF antagonist is selected from the group consisting of:
 - a) a polypeptide comprising an anti-M-CSF antibody;

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- b) a polypeptide comprising an anti-M-CSFR antibody thereof;
- c) a soluble polypeptide comprising an M-CSF mutein or derivative thereof; or
 - d) a soluble polypeptide comprising an M-CSFR mutein or derivative

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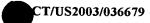
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- 95. The use according to claim 94 wherein said antibody is selected from the group consisting of:
 - a) a polyclonal antibody;
 - b) a monoclonal antibody;
 - c) a humanized antibody;
 - d) a human antibody;
 - e) a chimeric antibody;
 - f) Fab, F(ab')₂ or F_v antibody fragment; and
 - g) a mutein of any one of a) to f).
- 96. The use according to claims 82-85 wherein the therapeutic agent is a bisphosphonates.
 - 97. The use according to claim 96 wherein the bisphonate is zeledronate, pamidronate, clodronate, etidronate, tilundronate, alendronate, or ibandronate.
- 98. The use according to claims 82-85 wherin the therapeutic agent is a chemotherapeutic agent.
 - 99. The use according to claim 51 wherein the subject is precluded from receiving bisphophonate treatment.
 - 100. Use of a M-CSf antagonist in the manufacture of a medicament for reducing the dose of a therapeutic agent administered to a subject to treat or prevent bone metastases and tumor growth.
 - 101. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for preventing, in a subject afflicted with metastatic cancer, bone metastases and tumor growth.
 - 102. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for preventing, in a subject

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afflicted with metastatic cancer, bone loss associated with the cancer.

- 103. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for treating a metastatic cancer.
- 104. Use of a M-CSF antagonist, a therapeutic agent, and a non-M-CSF colony stimulating factor in the manufacture of a medicament for reducing the severity of bone loss associated with the cancer and inhibiting tumor growth in a subject afflicted with metastatic cancer.
 - 105. The use according to any one of claims 101-103 wherein the non-M-CSF colony stimulating factor is G-CSF.
- 106. Use of am antibody that specifically binds to the extracellular portion of membrane-bound M-CSF in the manufacture of a medicament for targeting a tumor cell that expresses membrane-bound M-CSf on its surface.
 - 107. Use of an antibody that (a) specifically binds to the extracellula portion of membrane-bound M-CSF, and (b) is conjugated to a radionuclide or other toxin in the manufacture of a medicament for treating cancer.
 - 108. The use of claim 107 wherein said antibody is selected from the group consisting of:
 - a) a polyclonal antibody;
 - b) a monoclonal antibody;
 - c) a humanized antibody;
 - d) a human antibody;
 - e) a chimeric antibody;
 - f) Fab, F(ab')₂ or F_v antibody fragment; and
 - g) a mutein of any one of a) to f).
- 25 Use of a non-murine anti-M-CSF antibody in the manufacture of a medicament for treating cancer.
 - 110. The use according to claim 109 wherein the cells comprising the cancer do not secrete M-CSF.
- 111. Use of a M-CSF antagonist, in an amount that is larger that the amount 30 effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament

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for preventing bone metastases.

- 112. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament for neutralizing M-CSF produced by a subject's cells.
- 113. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament for treating a subject afflicted with a metastatic cancer to bone.
 - 114. Use of a M-CSF antagonist, in an amount that is larger that the amount effective to neutralize M-CSF produced by cancer cells, in the manufacture of a medicament for treating cancer.